Imipramine in childhood enuresis: Further studies on the relationship of time of administration to effect

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A previous study[1] established that 25 mg. of imipramine (Tofranil, Geigy) given at 8 p.m. to children aged 6 to 12 years had its greatest effect on enuretic incidents occurring after 1 a.m. The same dose administered at 3.15 p.m. was chiefly effective in reducing enuretic incidents prior to 1 a.m. Nocturnal enuresis in "early enuretics" was much more effectively controlled by early than by late medication. In these subjects incidents before 1 a.m. formed a higher proportion of total incidents than in the "late enuretics" in whom late administration of the agent gave greatly superior results.

Greatest control resulted when 25 mg. of imipramine was given at 3.15 *and* 8 p.m. so that the dose was doubled. It was predicted that the maximal effect from 50 mg. would be obtained by relating the time of administration to the time of enuresis and not by using two separate doses of 25 mg. The testing of that hypothesis will be described.

Method

The enuretic subjects were eight boys and one girl, aged 7 years, 3 months to 10 years, 9 months (mean 8 years, 11 months), admitted for residential treatment because of serious acting-out behaviour disorders. In seven a diagnosis of "character disorder" was made. Two were schizophrenic but able to respond to the same therapeutic milieu. Four of these children were of average intelligence (I.Q. 90 to 109), four were low average (I.Q. 80 to 89) and one was borderline (I.Q. 70 to 79) as measured by the Wechsler intelligence scale for children.

A double-blind investigation was conducted using 25-mg. imipramine tablets and matching placebo. Three drug conditions were employed, each lasting four weeks: A: 25 mg. at 3.15 and 8 p.m.; B: 50 mg. at 3.15 p.m.; C: 50 mg. at 8 p.m. During the first four weeks no medication was given (N1). Subjects were randomly assigned to the six different drug condition sequences. Each drug condition was preceded by a four-week period during which placebo was given at the same time and in identical amount to the drug (Pa, Pb, Pc). Following the final drug condition, placebo was given for a further four weeks without altering time or dose schedule, and finally the subjects were kept under four weeks' observation without medication (N2). The trial therefore extended over 36 weeks and was completed by seven children. One remained for all but the final no-medication period and one was discharged after the second drug condition.

Child-care staff examined each patient for enuresis at 12.30 a.m. and 6.00 a.m. and if wet the time was noted. If a child awoke and reported enuresis, that time was recorded. Nights away from the hospital were excluded, as were days when medication was for any reason not received within 30 minutes of the correct time.

Results

For the total group, enuresis while taking the placebo occurred on 491 of a possible 814 nights or 60.32% and on 212 of 683 nights when the drug was given (31.04%). This is a reduction of 48.54% from the placebo level and is highly significant ($\chi^2 = 134.27$ $P = < .001$). The percentage of enuretic nights per child while on placebo varied from 20.55 to 77.78 (mean 56.45) and while on the drug from 2.63 to 50.62 (mean 30.38). Significant reductions were observed in six subjects ($P < .001$ in four and $< .01$ in two, χ^2 test).

Fig. 1 shows the enuresis per 100 nights for the whole group while on successive placebo or drug periods. P1 represents the first placebo administration, whether Pa, Pb or Pc; D2 the second drug period, whether A, B or C and so on. As had been observed previously,[2] there was a progressive decline in enuresis each time after drug administration, with a rapid return to initial levels at the end of the investigation. The total patient days per period is shown with χ^2 values and levels of significance of differences between periods calculated from the raw data. Enuresis declined significantly after each drug administration.

Fig. 2 shows the reduction in enuretic nights and incidents before and after 1 a.m. for the whole group on the three drug conditions. The shaded area in each column indicates the fall per 100 nights, the upper figure the actual decline and the lower figure the percentage reduction from the placebo level. It will be seen that early administration produced the largest fall in early incidents. Late incidents fell very slightly more on late medication although as a percentage of placebo level the decline was actually less than when medication was given early. The three drug conditions produced almost identical reductions in enuretic nights, with the lowest percentage fall for condition A.

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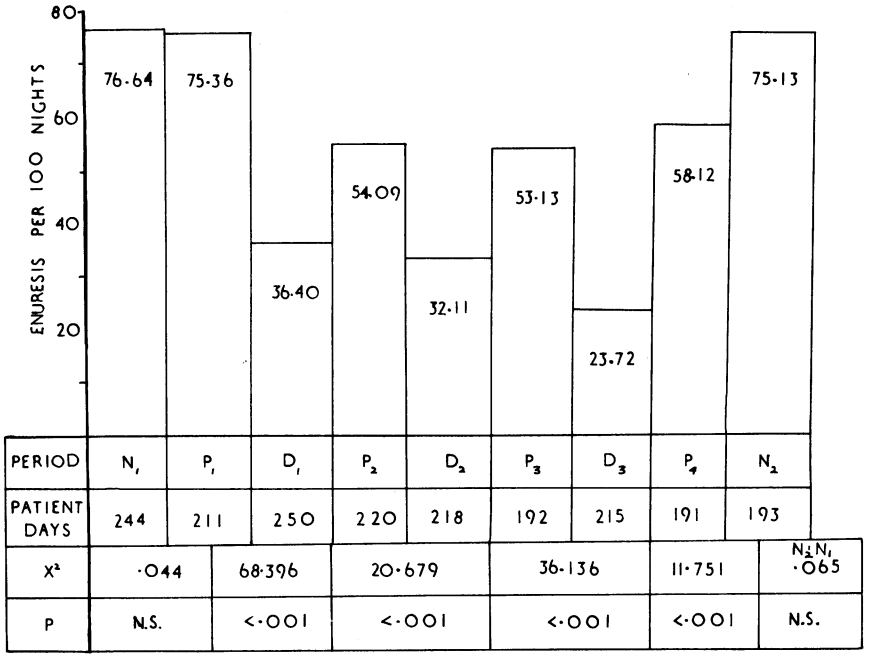

PERIOD	N_1	P_1	D_1	P_2	D_2	P_3	D_3	P_4	N_2
PATIENT DAYS	244	211	250	220	218	192	215	191	193
χ^2	·044		68·396	20·679		36·136		11·751	N_2N_1 ·065
P	N.S.		<·001	<·001		<·001		<·001	N.S.

FIG. 1—Enuresis per 100 nights for the total group for successive periods, patient-days per period, χ^2 values and levels of significance of differences between periods.

The levels of significance of these effects appear in Table I. Enuresis was significantly controlled by all three drug conditions, and only the fall in late incidents on condition A failed to reach the .05 level of significance.

For the whole group there was no significant difference in the effectiveness of the three drug conditions on enuretic nights ($\chi^2r = .25$, P = .967 Friedman Two-Way Analysis of Variance) or on incidents before 1 a.m. ($\chi^2r = 3.714$, P = .192) or after 1 a.m. ($\chi^2r = .286$, P = .964).

The proportion of incidents occurring before 1 a.m. did not significantly differ in the present group when compared with the subjects in the previous investigation (U = 34.5, P = > .05 Mann-Whitney U Test). The mean fall in enuretic nights per 100 nights on early medication (B) for the early enuretics was 39.43 and on late medication (C) 22.21. Condition C most reduced enuretic nights in the late enuretics (mean 25.47 per 100 nights), compared with 20.25 on condition B.

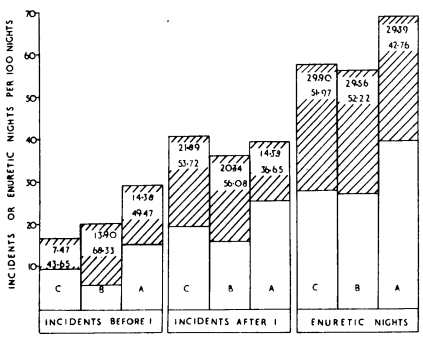

FIG. 2—Reduction in incidents before and after 1 a.m. and in enuretic nights per 100 nights on the three drug conditions. The shaded areas show the fall, the upper figures the actual reduction and the lower figures the percentage reduction from placebo level. A = 25 mg. at 3.15 and 8 p.m.; B = 50 mg. at 3.15 p.m.; C = 50 mg. at 8 p.m.

Early medication reduced enuretic nights more than late administration in only two of five "early enuretics", and late dosage had a greater effect in only one of four "late enuretics". The two groups did not significantly differ in their response to the time of medication (U = 9, P = .452 Mann-Whitney U Test). These findings were not materially affected by including the subject with the fifth highest proportion of early incidents in the group of late rather than early enuretics.

Discussion

Although the findings were in the predicted direction, the influence of time of medication was much less apparent than in the earlier investigation. On the higher dosage the effect of early administration was not lost later in the night. Whether the drug was given early or late, incidents after 1 a.m. were lowered to almost the same degree. Divided medication offered no advantages and the three conditions were not significantly different in their effectiveness on incidents or enuretic nights.

In the previous study early medication reduced enuresis by a mean of 19.01 nights per 100 days among the early enuretics and only .07 for the late group. Corresponding values on late medication were 4.91 and 25.47 respectively. Although there was a similar trend in this study, both early and late timing lowered enuresis in excess of 20 nights per 100 days in both groups.

When only 25 mg. of imipramine was given, five of six early enuretics had shown a greater fall in enuretic nights than when the same dose was given later, and the contrary was true among late enuretics. This clear difference between the groups in response to the time of medication reaches statistical significance (U = 5, P = .021 Mann-Whitney U Test). No such difference was present in this study.

TABLE I
Levels of signficance of reduction in enuretic incidents and nights for each drug condition (Wilcoxon matched pairs signed ranks test one tailed)

Drug condition	*Enuretic incidents* *Before 1 a.m.*	*After 1 a.m.*	*Enuretic nights*
A (25 mg. at 3.15 and 8 p.m.)	.01	n.s.	< .025
B (50 mg. at 3.15 p.m.)	.01	< .005	< .005
C (50 mg. at 8 p.m.)	.025	.025	.005

The most probable explanation for these findings is that on the smaller dose a longer time elapsed before an effective blood level was reached. When given early this level fell during the latter part of the night. With 50 mg. the concentration rises more rapidly and the necessary level is sustained long enough to control enuresis over a much longer period. As a result no significant advantage is obtained by relating time of administration of 50 mg. imipramine to time of enuresis.

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References

1. ALDERTON, H. R.: *Canad. Psychiat. Ass. J.*, 12: 197, 1967.
2. *Idem*: *Ibid.*, 10: 141, 1965.